ATLANTA

LUNG CANCER SYMPOSIUM

Novel Treatment Approaches in SCLC

Taofeek K. Owonikoko, MD, PhD

Date 10/28/2023

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DISCLOSURES

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17th Annual

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LUNG CANCER SYMPOSIUM

Frontline Treatment ES-SCLC

Antiangiogenic agents

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IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

Five-year survival in patients with ES-SCLC treated with atezolizumab in IMpower133: IMbrella A extension study results

Stephen V. Liu,[1] Rafal Dziadziuszko,[2] Shunichi Sugawara,[3] Steven Kao,[4] Maximilian Hochmair,[5] Florian Huemer,[6] Gilberto de Castro, Junior,[7] Libor Havel,[8] Reyes Bernabé Caro,[9] György Losonczy,[10] Jong-Seok Lee,[11] Dariusz Kowalski,[12] Zoran Andric,[13] Raffaele Califano,[14] Andrea Veatch,[15] Gregory Gerstner,[16] Marta Batus,[17] Stefanie Morris,[18] Monika Kaul,[19] Madeena Siddiqui,[19] Huafei Li,[20] Wei Zhang,[19] Brazin Nabet,[19] Martin Reck[21]

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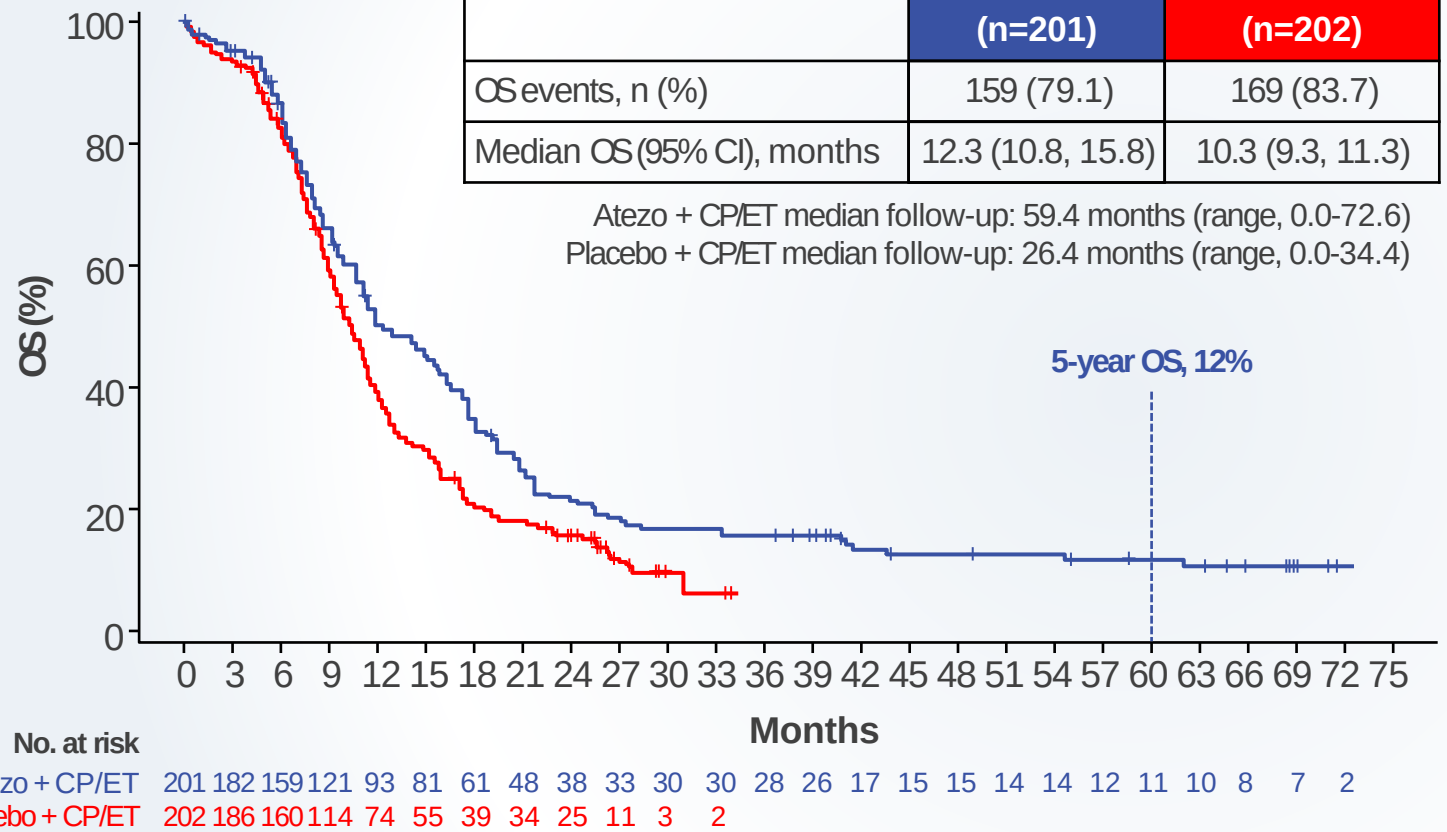
IMpower133 and IMbrella A: long-term OS

	Atezo + CP/ET (n=201)	Placebo + CP/ET (n=202)
OS events, n (%)	159 (79.1)	169 (83.7)
Median OS (95% CI), months	12.3 (10.8, 15.8)	10.3 (9.3, 11.3)

Atezo + CP/ET median follow-up: 59.4 months (range, 0.0-72.6)
Placebo + CP/ET median follow-up: 26.4 months (range, 0.0-34.4)



No. at risk

Atezo + CP/ET	201	182	159	121	93	81	61	48	38	33	30	30	28	26	17	15	15	14	14	12	11	10	8	7	2
Placebo + CP/ET	202	186	160	114	74	55	39	34	25	11	3	2													

OS rate (95% CI), %	IMpower133 and IMbrella A Atezo + CP/ET (n=201)	IMpower133 only Placebo + CP/ET (n=202)
1-year	52% (45-59)	39% (32-46)
2-year	22% (16-28)	16% (11-21)
3-year	16% (11-21)	NE[a]
4-year	13% (8-18)	NE[a]
5-year	12% (7-17)	NE[a]

Clinical cutoff date: 16 March 2023. NE, not estimable. [a] OS rates were NE in the control arm as rollover to IMbrella A was not permitted.

Benmelstobart with Anlotinib plus Chemotherapy as First-line Therapy for ES-SCLC: A Randomized, Double-blind, Phase III Trial (ETER701)

Ying Cheng[1], R. Yang[2], J. Chen[3], W. Zhang[4], C. Xie[5], Q. Hu[6], N. Zhou[7], C. Huang[8], S. Wei[9], H. Sun[10], X. Li[11], Y. Yu[12], J. Lai[13], H. Yang[14], H. Fang[15], H. Chen[16], P. Zhang[17], K. Gu[18], Q. Wang[19], J. Shi[20], T. Yi[21], X. Xu[22], X. Ye[23], D. Wang[24], C. Xie[25], C. Liu[26], Y. Zheng[27], D. Lin[28], W. Zhuang[29], P. Lu[30], G. Yu[31], J. Li[32], Y. Gu[33], B. Li[34], R. Wu[35], O. Jiang[36], Z. Wang[37], G. Wu[38], H. Lin[39], D. Zhong[40], Y. Xu[41], Y. Shu[42], D. Wu[43], X. Chen[44], J. Wang[45], M. Wang[46]

[1]**Jilin Cancer Hospital, Changchun**, [2]Yunnan Cancer Hospital, Kunming, [3]Hunan Cancer Hospital, Changsha, [4]The First Affiliated Hospital of Nanchang University, Nanchang, [5]Shandong Cancer Hospital and Institute, Jinan, [6]The Affiliated Hospital of Inner Mongolia University, Hohhot, [7]Sun Yat-sen University Cancer Center, Guangzhou, [8]Tianjin Medical University Cancer Institute and Hospital, Tianjin, [9]Gansu Provincial Cancer Hospital, Lanzhou, [10]The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, [11]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, [12]Harbin Medical University Cancer Hospital, Harbin, [13]Fujian Medical University Union Hospital, Fuzhou, [14]Xiangya Hospital Central South University, Changsha, [15]Anhui Chest Hospital, Hefei, [16]Affiliated Hospital of Guangdong Medical University, Zhanjiang, [17]Shanghai Pulmonary Hospital, Shanghai, [18]The First Affiliated Hospital of Anhui Medical University, Hefei, [19]Henan Cancer Hospital, Zhengzhou, [20]Linyi Cancer Hospital, Linyi, [21]Xiangyang Central Hospital, Xiangyang, [22]Northern Jiangsu People's Hospital, Yangzhou, [23]Guizhou Provincial People's Hospital, Guiyang, [24]Hengshui People's Hospital, Hengshui, [25]Zhongnan Hospital of Wuhan University, Wuhan, [26]Cancer Hospital Affiliated to Xinjiang Medical University, Urumqi, [27]The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, [28]Jiangmen Central Hospital, Jiangmen, [29]Fujian Cancer Hospital, Fuzhou, [30]The First Affiliated Hospital of Xinxiang Medical College, Xinxiang, [31]Weifang People's Hospital, Weifang, [32]Qinghai University Affiliated Hospital, Xining, [33]Qinghai Provincial People's Hospital, Xining, [34]Beijing Chest Hospital, Capital Medical University, Beijing, [35]Shengjing Hospital of China Medical University, Shenyang, [36]The Second People's Hospital of Neijiang, Neijiang ,[37]The First Affiliated Hospital of Xinjiang Medical University, Urumchi, [38]Meizhou People's Hospital, Meizhou, [39]The Second Affiliated Hospital of Hainan Medical University, Haikou, [40]Tianjin Medical University General Hospital, Tianjin/CN ,41Jingzhou Central Hospital, Jingzhou, [42]Jiangsu Province Hospital, Nanjing, [43]Shenzhen People's Hospital, Shenzhen, [44]The First Affiliated Hospital of Wannan Medical College, Wuhu, [45]Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, [46]Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou

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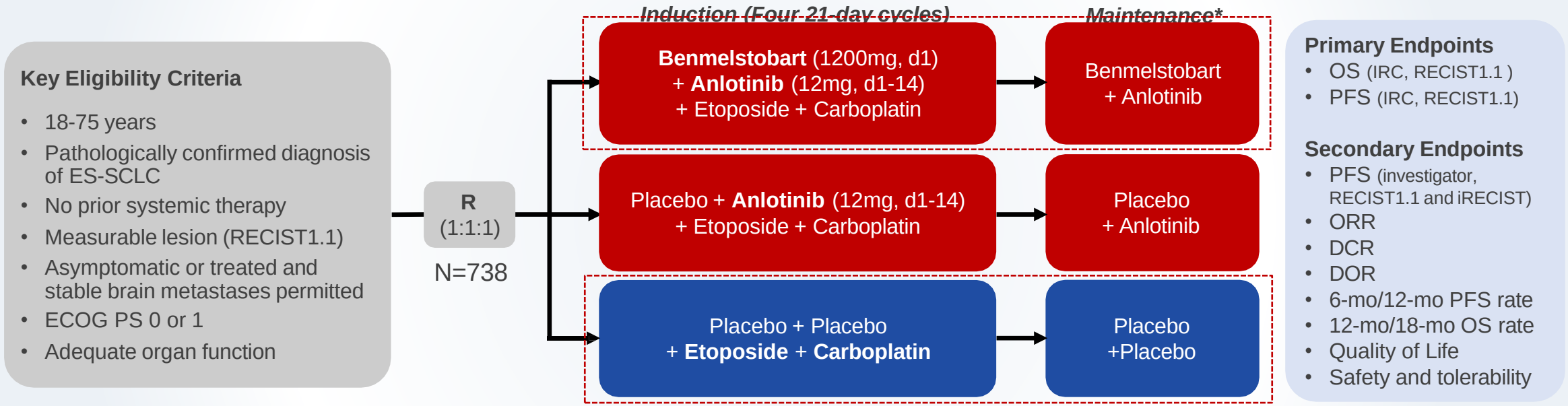
Study Design

- A multicenter, placebo-controlled, randomized phase III trial in first-line ES-SCLC.

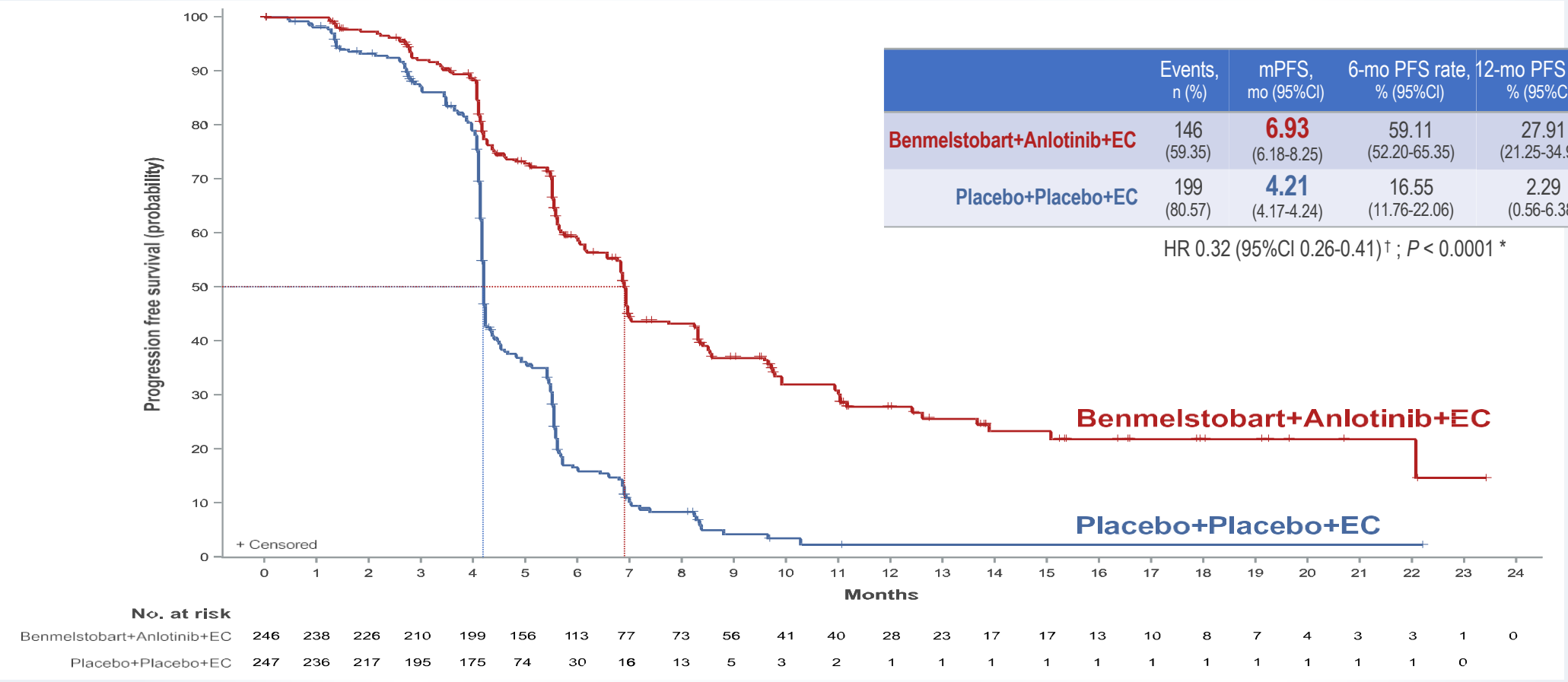


- **Stratified by:** ECOG PS (0/1); brain metastases (Y/N); liver metastases (Y/N).
- **Statistical Consideration**

  - The primary efficacy endpoints of this trial are PFS and OS. In this study, a fixed-sequence test will be used for comparisons between treatment groups.
  - The previous study showed that the median OS and PFS in the control group were 10 and 4 months, respectively. Patients were enrolled within a 12-month accrual period with an 18-month follow-up and were randomly assigned (1:1:1) to three groups. The power was 85% with a type I error rate of 0.050 and a dropout incidence of 10%. The type I error rate in the interim analysis for PFS will be controlled by the Method Based on the Sum of P-values (MSP). The initial sample size in this study will be estimated based on PFS using a computer simulation program.

* During maintenance therapy, patients are allowed to receive PCI, but not thoracic radiation.

Primary Endpoint: PFS (ITT Population)

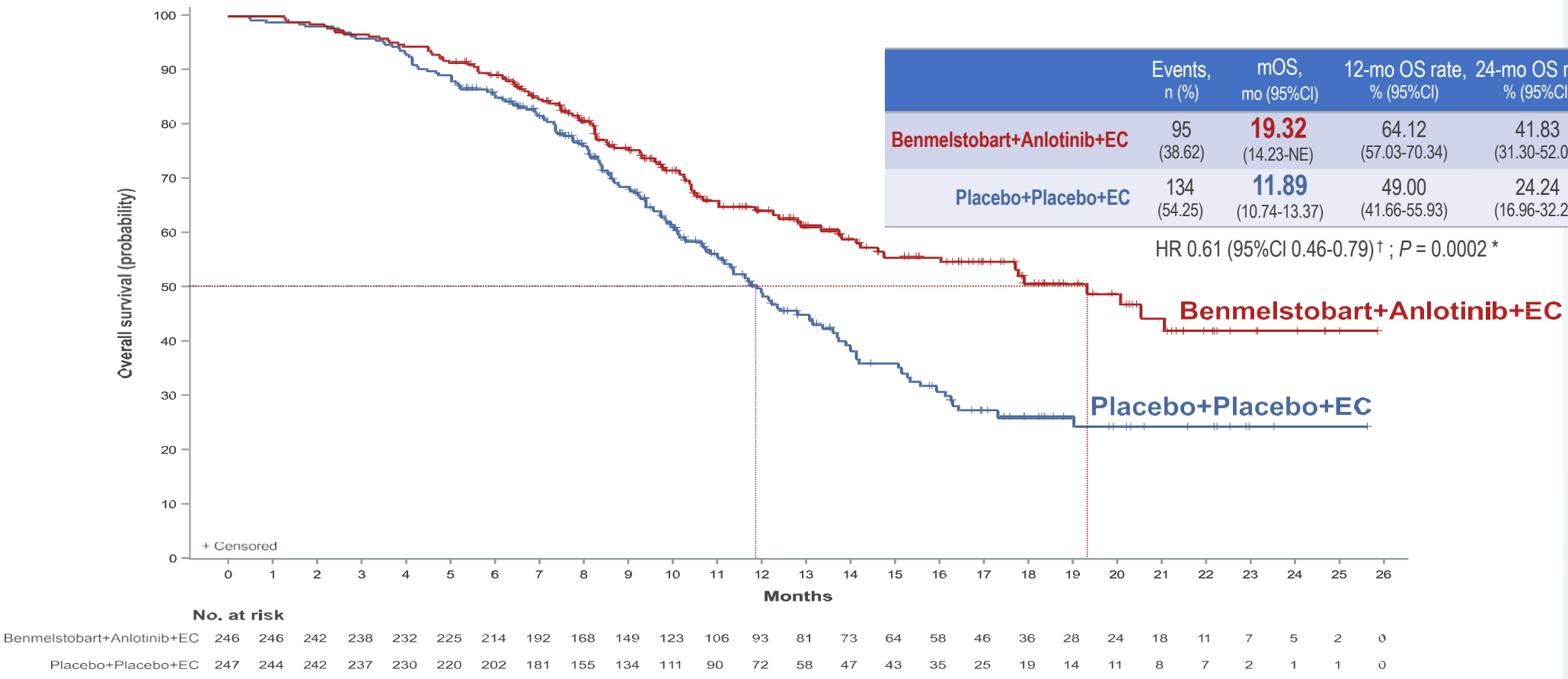


	Events, n (%)	mPFS, mo (95%CI)	6-mo PFS rate, % (95%CI)	12-mo PFS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	146 (59.35)	**6.93** (6.18-8.25)	59.11 (52.20-65.35)	27.91 (21.25-34.94)
Placebo+Placebo+EC	199 (80.57)	**4.21** (4.17-4.24)	16.55 (11.76-22.06)	2.29 (0.56-6.38)

HR 0.32 (95%CI 0.26-0.41)† ; *P* < 0.0001 *

Data cutoff date: May 14, 2022; median follow-up was 14.0 months (range, 12.8-15.5).
*P value in sensitivity analysis was done using unstratified log-rank test. †Hazard ratios (HR) in sensitivity analysis was estimated using unadjusted Cox proportional hazards model.

Primary Endpoint: OS (ITT Population)



	Events, n (%)	mOS, mo (95%CI)	12-mo OS rate, % (95%CI)	24-mo OS rate, % (95%CI)
Benmelstobart+Anlotinib+EC	95 (38.62)	**19.32** (14.23-NE)	64.12 (57.03-70.34)	41.83 (31.30-52.00)
Placebo+Placebo+EC	134 (54.25)	**11.89** (10.74-13.37)	49.00 (41.66-55.93)	24.24 (16.96-32.26)

HR 0.61 (95%CI 0.46-0.79)† ; *P* = 0.0002 *

Data cutoff date: May 14, 2022; median follow-up was 14.0 months (range, 12.8-15.5).
*P value in sensitivity analysis was done using unstratified log-rank test. †Hazard ratios (HR) in sensitivity analysis was estimated using unadjusted Cox proportional hazards model.

Carboplatin, Etoposide, Bevacizumab, and Atezolizumab in Patients with Extensive- Stage SCLC – GOIRC-01-2019 ML41241
CeLEBrATE Trial

Giuseppe Lamberti, MD, PhD
Università di Bologna Italy

Investigator-initiated Italian multicentric single-arm phase II trial (15 Centers)

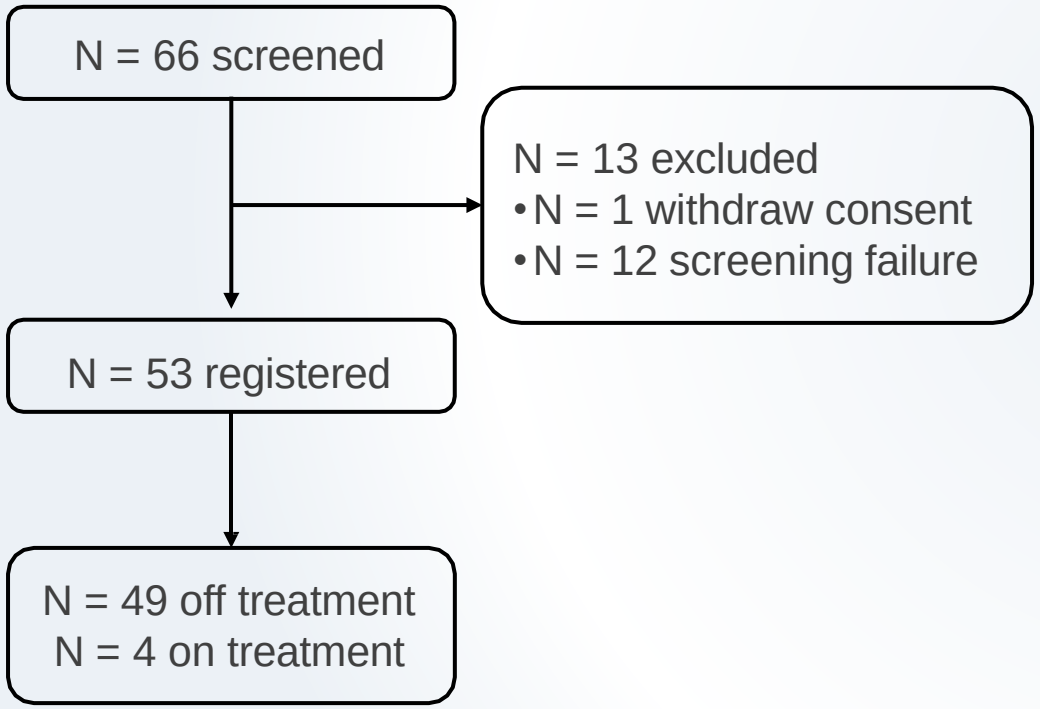
EudraCT 2019-003798-25

Statistical design:
Alternative hypothesis: 1-year OS >70%;
Null hypothesis: 1-year OS <50%;
Type I error rate of 5% (one-sided)
Power of 90%
Estimated N = 53

Results – study population

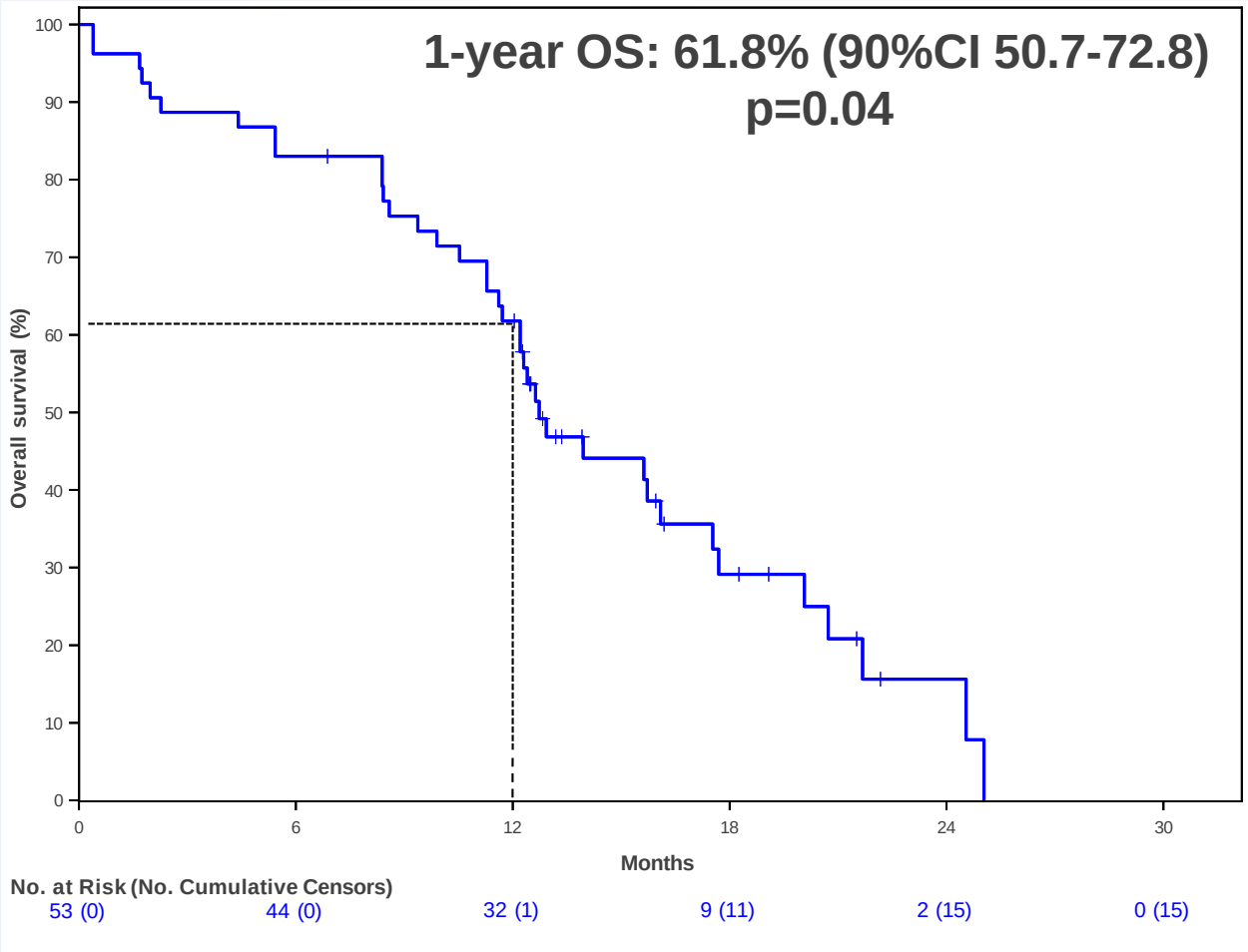
Enrolment: 08/2020 – 03/2022

Data cutoff: 31/03/2023



Patient characteristics		N=53	(%)
Sex	Female	24	(45.3%)
	Male	29	(54.7%)
Age	Median (range)	65 years	(46 – 79)
Smoking status	Active	24	(45.3%)
	Former	26	(49.1%)
	Never	1	(1.9%)
	Unknown	2	(3.8%)
ECOG PS	0	31	(58.5%)
	1	22	(41.5%)
Metastatic sites	Brain	10	(18.9%)
	Liver	14	(26.4%)
Sum of longest diameter	Median (range)	119.5 mm	(17 – 240)

Primary endpoint - Overall survival



Median follow-up: 19.1 months (95%CI 13.4-22.2)

Median OS: 12.7 months (95%CI 11.6-16.1)

38 patients died:

- PD: 32
- Toxicity: 4
- Other: 2

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Relapsed SCLC

Anti-DLL3 BiTE and ADCs

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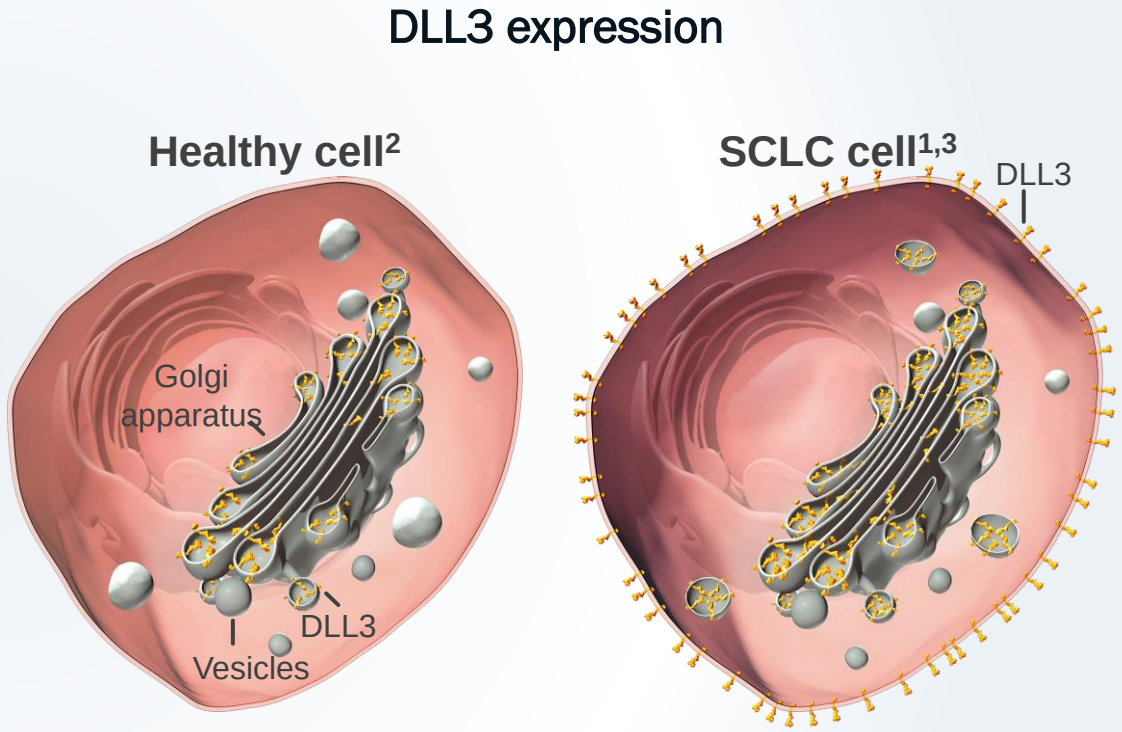
Delta-like ligand 3 (DLL3) is expressed on the cell surface of SCLC and rarely on normal cells

DLL3 is an inhibitory protein of Notch signaling, a pathway that is involved in embryonic development and neuroendocrine cell differentiation[1]

In healthy cells, DLL3 is typically located in the Golgi apparatus and cytoplasmic vesicles, and is rarely found on the cellular surface[2]

In high-grade neuroendocrine cancers, including SCLC, DLL3 is expressed on the cell surface[1]

~85-94% of patients with SCLC express DLL3[3,4,*]



DLL3 is a tumor-associated antigen and a potential target for T-cell engagers

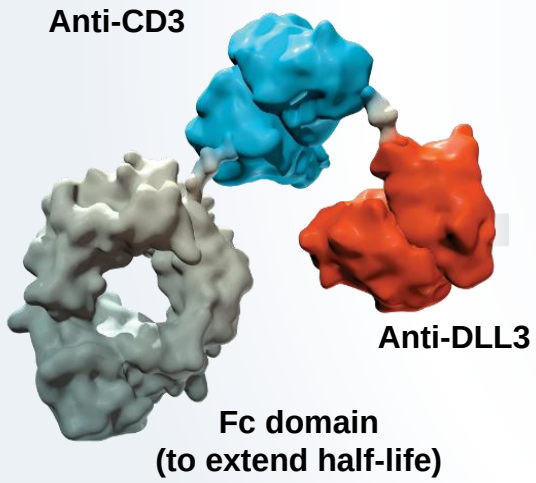
1. Sabari JK, et al. Nat Rev Clin Oncol 2017;14:549–61; 2. Leonetti A, et al. Cell Oncol (Dordr) 2019;42:261–73; 3. Rojo F, et al. Lung Cancer 2020;147:237–43; 4. Paz-Arez L, et al. J Clin Oncol 2023;41:2893–903.

*Based on a study where presence of DLL3 staining could be punctate and/or diffuse cytoplasmic and/or partial or circumferential membranous staining, and a study that evaluated surface DLL3 expression.[3,4]

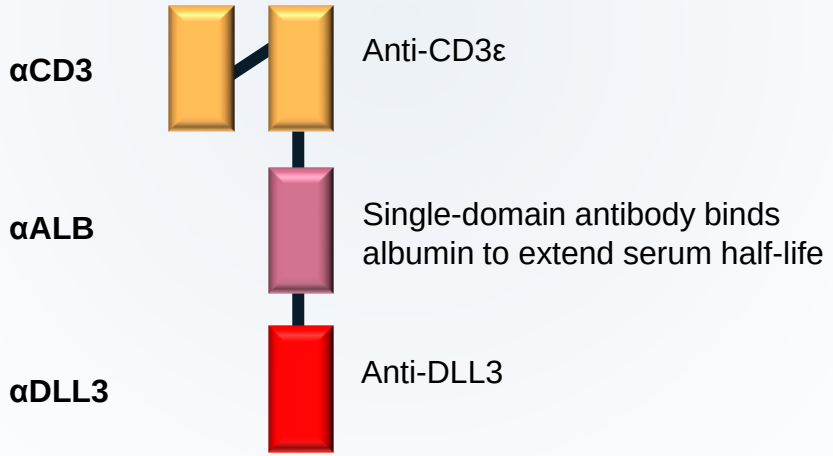
BiTE®, Bispecific T-cell Engager; DLL3, delta-like ligand 3; SCLC, small cell lung cancer.

Selected investigational T-cell engagers targeting DLL3

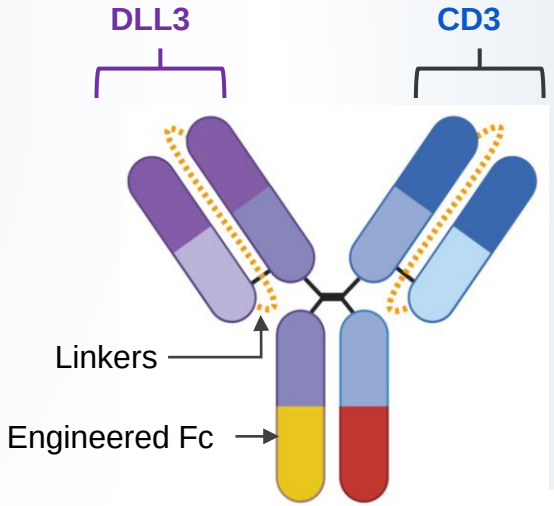
Tarlatamab
Half-life extended BiTE molecule
(bispecific T-cell engager)
Phase 2/3[1,2]



HPN328
TriTAC (trispecific
T cell-activating construct)
Phase 1/2[3,4]



BI 764532
Bispecific mAb
Phase 1/2[5–7]



1. Paz-Ares L, at al. ASCO 2023; poster 232a; 2. ClinicalTrials.gov, NCT05060016 (accessed August 2023);
3. Aaron W, et al. AACR-NCI-EORTC International Conference 2019; abstract C033;
4. Clinicaltrials.gov, NCT04471727 (accessed June 2023); 5. Wermke M, et al. Future Oncol 2022;18:2639–49;
6. Wermke M, et al. ASCO 2023; abstract 8502; 7. ClinicalTrials.gov, NCT05882058 (accessed June 2023).

αALB, anti-albumin; IgG, immunoglobulin G; mAb, monoclonal antibody; scFv, single-chain variable fragment.

Phase 1 DeLLphi-300: tarlatamab in relapsed/refractory SCLC

Study design

Clinicaltrials.gov identifier: NCT03319940

Key eligibility criteria

- Histologically or cytologically confirmed SCLC
- Progressed or recurred following **≥1 platinum-based chemotherapy** (including PD-L1 inhibitor if SOC)
- ≥2 measurable lesions
- ECOG PS: 0–2
- If present, clinically/radiologically stable brain metastases following treatment

Dose exploration (0.003 mg–100 mg)

Dose expansion

- Tarlatamab administered by IV infusion Q2W
- Step-dosing starting with the 3 mg cohort (1 mg followed by target dose on day 8, day 15, and Q2W thereafter)

Primary endpoint: safety including DLTs, TEAEs, and TRAEs
Key secondary endpoints: ORR, DOR, TTR, PFS, OS, and PK
Exploratory endpoint: evaluate immunogenicity, target protein expression and clinical benefit

Data cut-off: 19 July 2022

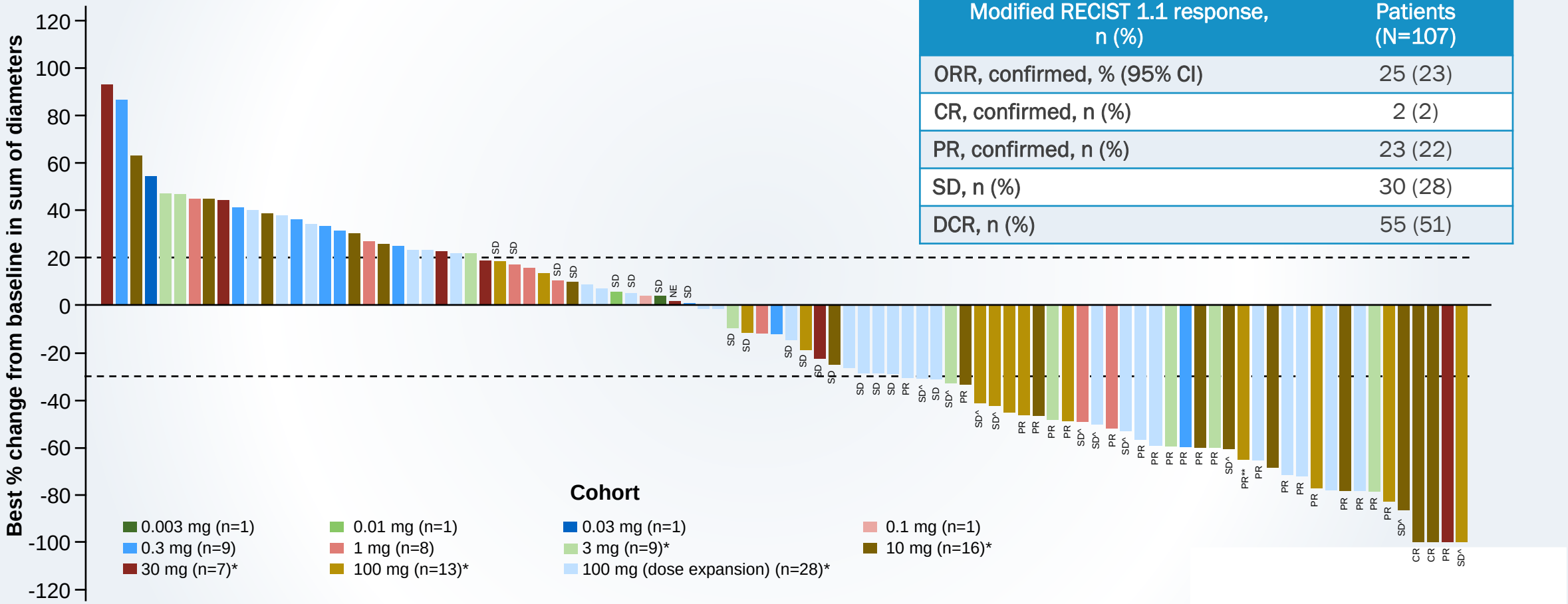
DLT, dose-limiting toxicity; DOR, duration of response; ECOG, European Cooperative Oncology Group Performance Status; IV, intravenous; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q2W, once in every two weeks; RP2D, recommended Phase 2 dose; SOC, standard-of-care; TTR, time to response.

Paz-Ares L, et al. J Clin Oncol 2023;41:2893–903.

Phase 1 DeLLphi-300: tarlatamab in relapsed/refractory SCLC

Anti-tumor activity

Modified RECIST 1.1 response, n (%)	Patients (N=107)
ORR, confirmed, % (95% CI)	25 (23)
CR, confirmed, n (%)	2 (2)
PR, confirmed, n (%)	23 (22)
SD, n (%)	30 (28)
DCR, n (%)	55 (51)



Data cut-off 19 July 2022; median follow-up: 8.7 months (range 0.2–31.8)

Best percent change from baseline in tumor burden (defined by the sum of the longest diameters of all target lesions) in 94 patients whose data cutoff date is at least 9 weeks after the first dose date and for whom postbaseline tumor data were available. Unlabeled bars include confirmed and unconfirmed PD.

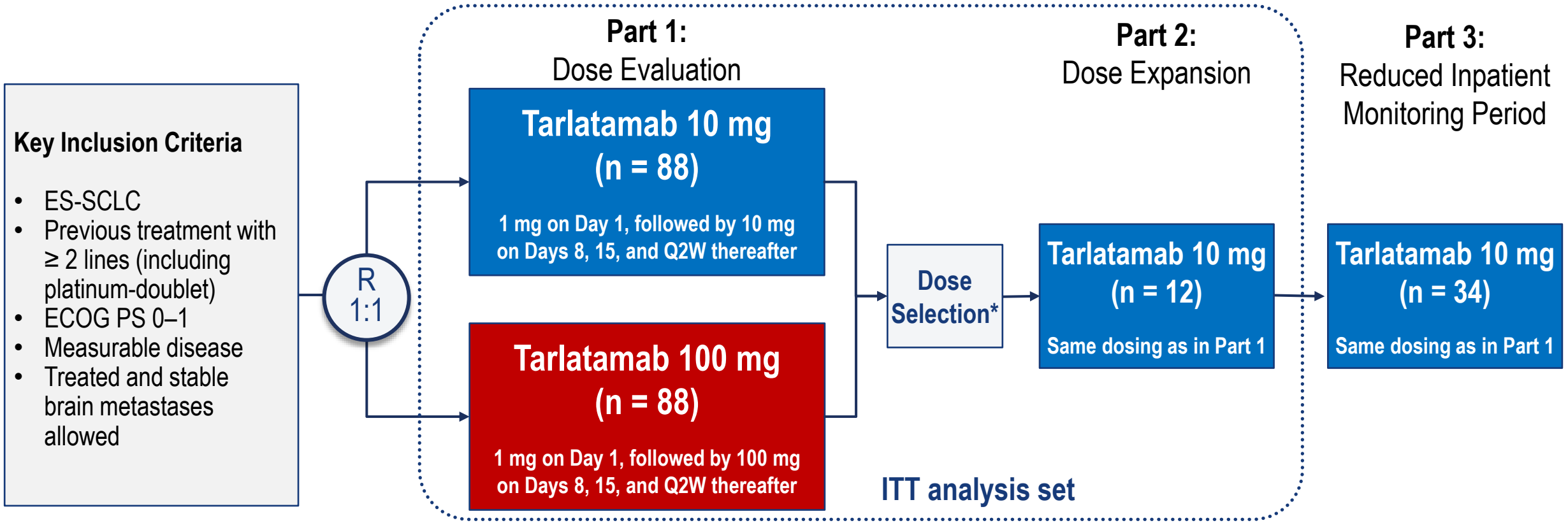
SD^ indicates patients had an initial response but did not have confirmation of response on the subsequent scan; PR** indicates patients had an initial PR and still have potential for future confirmative scans.

*Indicates step dosing (i.e., 1 mg run-in dose) was used in these cohorts; CR, complete response; DCR, disease control rate; NE, not estimable; PD, progressive disease; PR, partial response; **RECIST, Response Evaluation Criteria in Solid Tumors**; SD, stable disease.

Paz-Ares L, et al. J Clin Oncol 2023;41:2893–903.

DeLLphi-301 Study Design

Phase 2, open-label study (NCT05060016)



Primary Endpoint: ORR per RECIST v1.1 by BICR, TEAEs, tarlatamab serum concentrations

Secondary Endpoints Included: DOR, DCR, PFS per RECIST v1.1 by BICR, OS

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*Once 30 patients per dose level had the opportunity to confirm an objective response after the first post-treatment scan or ≥ 13 weeks of follow-up, whichever occurred first.
BICR, blinded independent central review; **DCR**, disease control rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ES-SCLC**, extensive stage-small cell lung cancer; **ITT**, intention-to-treat; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomization; **RECIST**, Response Evaluation Criteria in Solid Tumors; **TEAE**, treatment-emergent adverse event.

Baseline Characteristics

	Part 1 + 2 Tarlatamab 10 mg (n = 100)	Part 1 Tarlatamab 100 mg (n = 88)	Part 3 Tarlatamab 10 mg (n = 34)
Median age, years (range)	64 (35–82)	62 (34–80)	66 (49–80)
Male, %	72	70	71
Asian / Black or African American / White,* %	41 / 0 / 58	41 / 0 / 58	6 / 3 / 91
Ever smoker / non-smoker, %	92 / 8	94 / 6	97 / 3
ECOG performance status: 0 / 1, %	26 / 74	27 / 73	29 / 71
Prior lines of therapy, median (range)	2 (1–6)	2 (1–8)	2 (2–6)
2 prior lines of therapy, %	65	55	65
≥ 3 prior lines of therapy, %	33	43	35
Prior anti-PD-(L)1 treatment, %	73	70	82
< 90 days to progression after first-line platinum therapy,† %	28	20	21
Brain / liver metastases, %	23 / 39	36 / 34	12 / 35
DLL3 expression (> 0%), n/N evaluable (%)	80/83 (96)	71/74 (96)	N/A‡

Data cutoff, June 27, 2023. Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg.
*No patients of American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander race were enrolled.
†Platinum sensitivity was calculated as end of first-line platinum therapy to date of first progression.
‡DLL3 sample analysis from Part 3 in progress.
DLL3, delta-like ligand 3; **ECOG**, Eastern Cooperative Oncology Group; **N/A**, not available; **PD-(L)1**, programmed death 1 / ligand 1.

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Tarlatamab Anti-Tumor Activity

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Objective response rate, n (%) (97.5% CI)	40 (40.0) (29.1, 51.7)	28 (31.8) (21.1, 44.1)
Complete response	1 (1)	7 (8)
Partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable / no post-baseline scan*	10 (10)	20 (23)
Observed duration of response ≥ 6 months, n/N (%)	23/40 (58)	17/28 (61)
Disease control rate, n (%) (95% CI)	70 (70.0) (60.0, 78.8)	55 (62.5) (51.5, 72.6)

Tarlatamab 10 mg demonstrated anti-tumor activity in heavily pre-treated SCLC with an objective response rate of 40%

Data cutoff, June 27, 2023. Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 188). Part 3 did not have adequate follow-up for response analysis.
*Not evaluable and no post-baseline scan were considered non-responders for response analysis. **SCLC**, small cell lung cancer.

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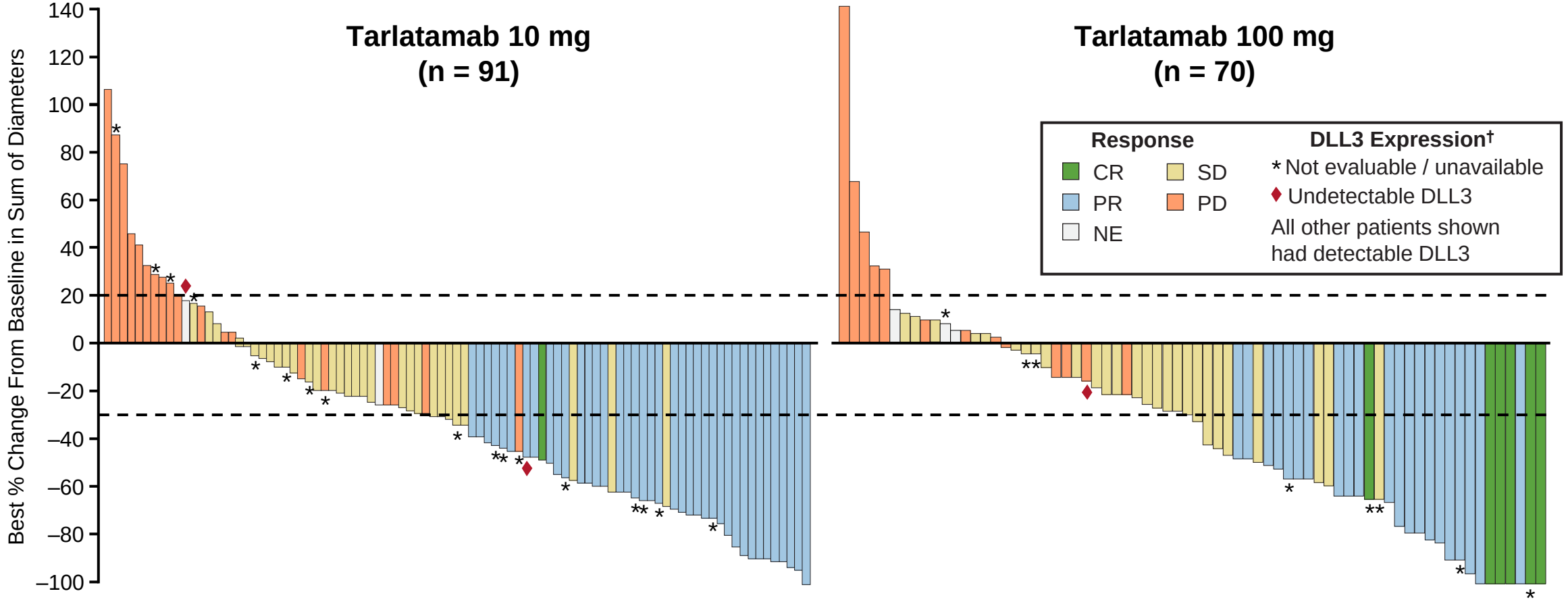
Anti-tumor Activity



Responses were observed regardless of DLL3 expression, as well as in patients without evaluable tumor tissue

Shown are 91 of 100 patients (tarlatamab 10 mg) and 70 of 88 patients (tarlatamab 100 mg) who had available post-baseline measurements of target lesions.
†DLL3 expression was assessed by immunohistochemistry of tumor tissue samples.
CR, complete response; **DLL3,** delta-like ligand 3; **NE,** not evaluable; **PD,** progressive disease, **PR,** partial response; **SD,** stable disease.

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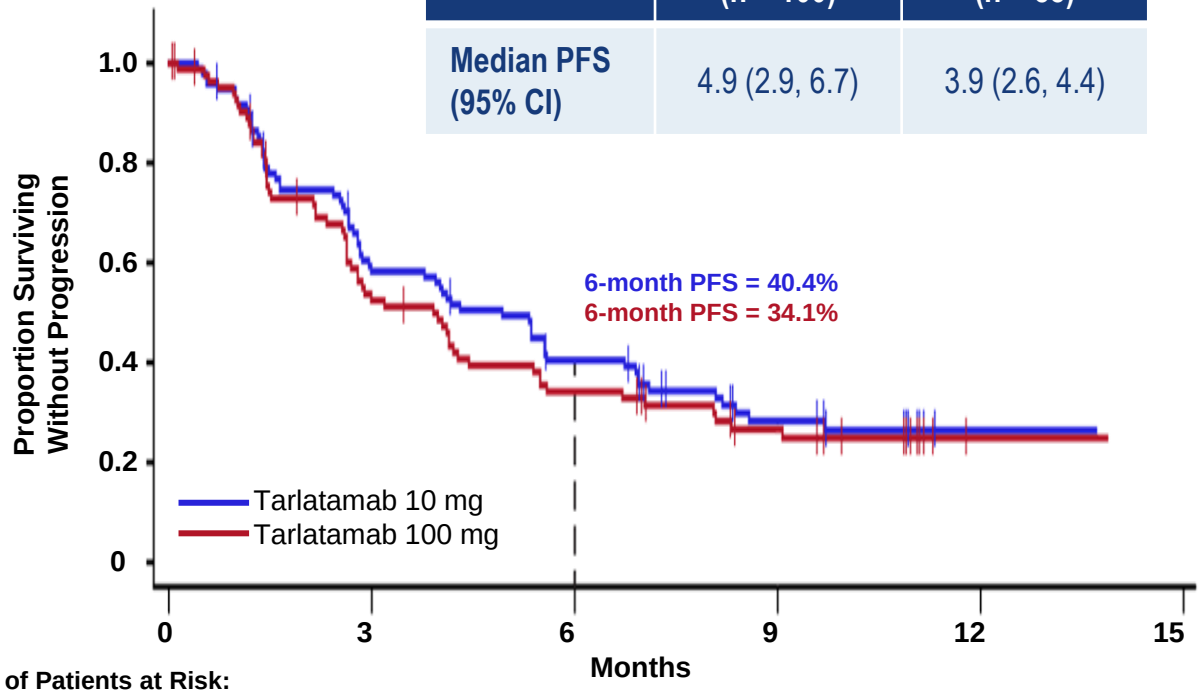
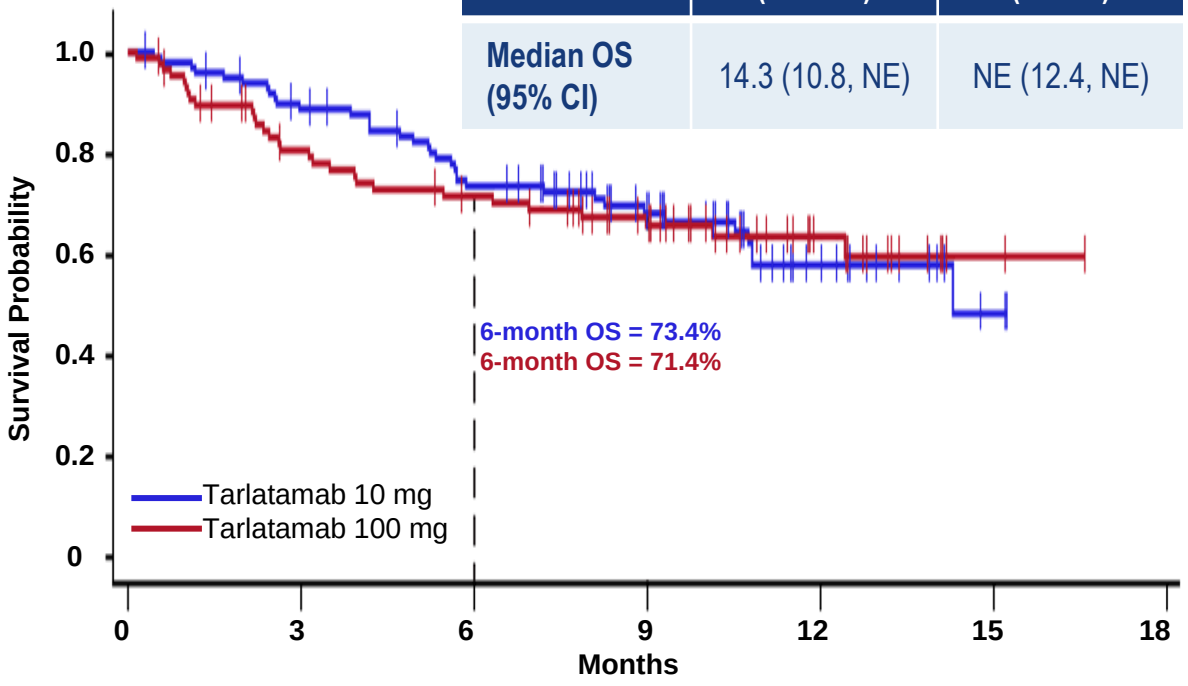
PFS and OS

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median PFS (95% CI)	4.9 (2.9, 6.7)	3.9 (2.6, 4.4)



Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median OS (95% CI)	14.3 (10.8, NE)	NE (12.4, NE)



Number of Patients at Risk:

Tarlatamab 10 mg	100	53	35	18	2	0	100	84	67	44	17	3	0
Tarlatamab 100 mg	88	41	26	15	3	0	88	62	53	39	16	2	0

OS data is not yet mature; at the last follow-up, 57% of patients in the tarlatamab 10 mg group and 51% of patients in the tarlatamab 100 mg group were still alive

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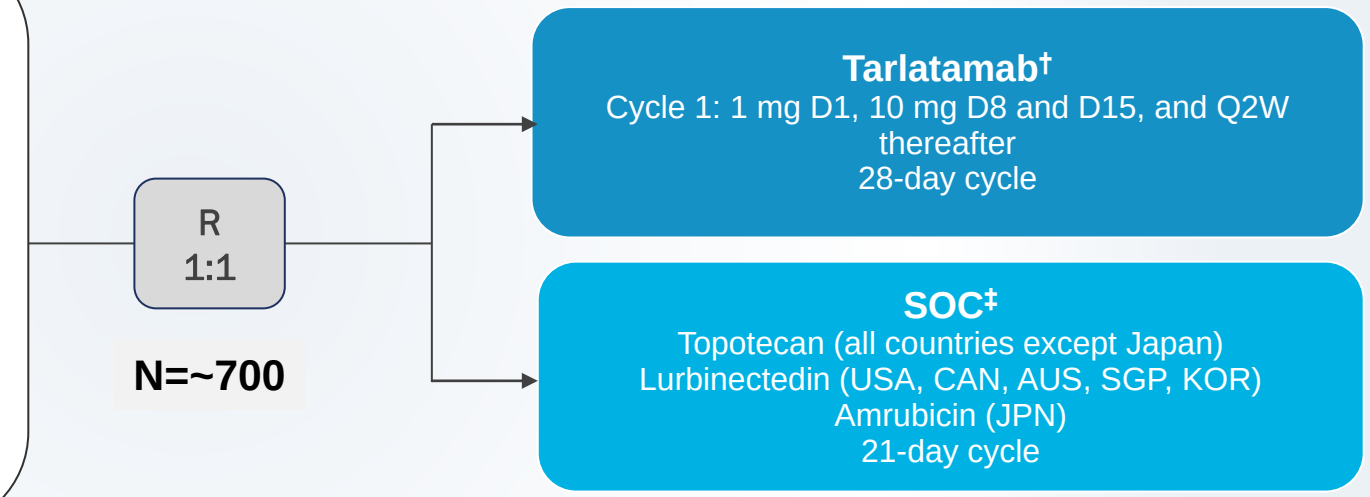
Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg.
NE, not estimable; **OS**, overall survival; **PFS**, progression-free survival.

Phase 3 DeLLphi-304: tarlatamab vs SOC in relapsed SCLC

Clinicaltrials.gov identifier: NCT05740566

Key eligibility criteria

- Histologically or cytologically confirmed SCLC
- Progressed or recurred following **1 platinum-based chemotherapy (including PD-L1 inhibitor if SOC)**
- Evaluable tumor sample for central testing
- Measurable disease as defined per RECIST 1.1
- ECOG PS: 0–1



Primary endpoint: OS
Secondary endpoints*: PFS, PROs, ORR, DCR, DOR, PK, TEAEs
Exploratory endpoint: quantification of relevant SCLC biomarker expression

*Other secondary endpoints include: OS rate at 1 year, 2 years, and 3 years from randomization, PFS at 1 year from randomization, immunogenicity of tarlatamab, time to deterioration (TTD) of symptoms.
†Administered as a 60-minute IV infusion. ‡SOC (21-day cycle): Lurbinectedin (USA, CAN, AUS, SGP, and KOR) will be administered as 3.2 mg/m² IV on day 1 every 3 weeks. Topotecan (all countries, except JPN and CHN) will be administered as IV at 1.5 mg/m² or oral at 2.3 mg/m²/day on days 1, 2, 3, 4, and 5 every 3 weeks. Topotecan (CHN) will be administered as IV at 1.25 mg/m² or oral at 2.3 mg/m2/day on days 1, 2, 3, 4, and 5 every 3 weeks.
Amrubicin (JPN) will be administered as 40 mg/m² IV on days 1 to 3 every 3 weeks.
DCR, disease control rate; PRO, patient-reported outcome.

1. ClinicalTrials.gov, NCT05740566 (accessed June 2023);
2. Paz-Ares L, at al. ASCO 2023; poster 232a.

Overview of ongoing tarlatamab trials in SCLC

Clinical trial name	Phase	Tarlatamab treatment	Status*
DeLLphi-300[1,2]	1	Tarlatamab in relapsed/refractory SCLC	Recruiting
DeLLphi-301[3]	2	Tarlatamab in heavily pretreated† patients with SCLC†	Active, not recruiting
DeLLphi-302[4,5]	1b	Tarlatamab in combination with an anti-PD1 monoclonal antibody in SCLC (2L or later)	Active, not recruiting
DeLLphi-303[6,7]	1b	Tarlatamab in combination with SOC in 1L ES-SCLC	Recruiting
DeLLphi-304[8,9]	3	Tarlatamab vs SOC chemotherapy in 2L SCLC	Recruiting

1. ClinicalTrials.gov, NCT03319940 (accessed June 2023); 2. Paz-Ares L, et al. J Clin Oncol 2023;41:2893–903;
3. ClinicalTrials.gov, NCT05060016 (accessed June 2023); 4. ClinicalTrials.gov, NCT04885998 (accessed June 2023);
5. Dowlati A, et al. Ann Oncol 2021;32(suppl_5):S1164–74.10.1016; 6. ClinicalTrials.gov, NCT05361395 (accessed June 2023);
7. Gadgeel SM, et al. Ann Oncol 2022;33(suppl_7):S701–2.10.1016; 8. ClinicalTrials.gov, NCT05740566 (accessed June 2023);
9. Paz-Ares L, at al. ASCO 2023; poster 232a.

*According to ClinicalTrials.gov.
†≥2 prior lines of treatment.
1L, first line therapy; 2L, second line therapy.

HPN328 Phase 1/2 trial: dose exploration and monotherapy/combination therapy in relapsed/refractory SCLC

Clinicaltrials.gov identifier: NCT04471727

Key eligibility criteria[1]

- Histologically or cytologically confirmed SCLC associated with DLL3 expression
- Progressed or recurred following **1 line of systemic therapy including platinum-based chemotherapy**
- Evaluable tumor sample for central testing

Phase 1

Dose exploration (8 dosing cohorts: 0.015–12.0 mg)[2]

N=18
(as of 21 April 2022)[3]

Phase 2

Combination therapy with atezolizumab

Phase 1
Primary endpoints[2]: safety, tolerability, determination of MTD/RP2D
Key secondary endpoints[2]: PK/PD, immunogenicity, preliminary anti-tumor activity (RECIST 1.1)

1. ClinicalTrials.gov, NCT04471727 (accessed August 2022); 2. Johnson ML, et al. ASCO 2022; abstract 8566;
3. Harpoon Therapeutics. Press release. Available at: https://ir.harpoontx.com/news-releases/news-release-details/harpoon-presents-interim-data-ongoing-dose-escalation-portion-t (accessed August 2023).

RP2D, recommended Phase 2 dose.

HPN328 Phase 1/2 trial: interim data

Recruitment

- 18 patients enrolled so far as of April 21, 2022, including 11 patients with SCLC

Safety

- Well tolerated; Grade 1–2 CRS reported in 22% of patients
- No dose-limiting toxicities or Grade 3+ CRS or ICANS events observed

Efficacy

- 3/11 patients with SCLC across all dose cohorts showed ≥30% target lesion reduction
- 4/6 SCLC patients receiving ≥1.215 mg HPN328 QW showed target lesion reduction
- Included one partial response with a 53% target lesion reduction at week 10 who previously achieved best overall response of stable disease on platinum-based chemo-immunotherapy

1 Press release. Available at: https://ir.harpoontx.com/news-releases/news-release-details/harpoon-presents-interim-data-ongoing-dose-escalation-portion-t (accessed August 2023).

BI 764532 Phase 1 trial: dose exploration in patients with SCLC or other DLL3-positive neuroendocrine cancers

Clinicaltrials.gov identifier: NCT04429087

Key eligibility criteria[1]

- Histologically confirmed SCLC or neuroendocrine carcinomas associated with DLL3 expression
- Failed or not eligible for standard therapies* according to local guidelines
- ECOG PS 0–1
- ≥1 evaluable lesion outside of CNS (per RECIST v1.1)

Dose exploration[1,2]

N=90
(as of 28 December 2022)[2]

Regimen A
8 dose levels
Fixed dose Q3W

Regimen B1
3 dose levels
Fixed dose QW

Regimen B2
6 dose levels
Step-in doses followed by a fixed dose QW

Phase 1a[1,2]
Primary endpoint: determination of MTD/RP2D
Key secondary endpoints: objective response (RECIST v1.1), PK/PD, safety, tolerability

1. Wermke M, et al. Future Oncol 2022;18:2639–49; 2. Wermke M, et al. ASCO 2023; abstract 8502.

*includes at least one line of chemotherapy and platinum-based chemotherapy for SCLC.

BI 764532 Phase 1 trial: interim data

Recruitment

- As of December 28, 2022, 90 patients received ≥1 dose of BI 764532[1]

Safety

- Dose-limiting toxicities were observed in 1 patient on regimen A (Grade 3 confusion) and 4 patients on regimen B2 (Grade 3–4 CRS, Grade 3 nervous system disorder, Grade 2 infusion-related reaction)
- Most common TRAEs were CRS, pyrexia, decreased lymphocytes, asthenia, and dysgeusia
- MTD has not yet been reached and dose escalation is ongoing

Efficacy

- In patients with SCLC (n=24) or NEC (n=23) who received the target dose of BI 764532, ORR was 33% and 22% across all regimens, respectively
- One patient with LCNEC was also evaluable for response and achieved partial response

*includes at least one line of chemotherapy and platinum-based chemotherapy for SCLC
LCNEC, large cell NEC.

Wermke M, et al. ASCO 2023; abstract 8502.

Other ongoing BI 764532 trials in SCLC

Clinical trial name or identifier	Phase	Study objective/treatment	Status*
NCT05879978[1]	1	BI 764532 in combination with ezabenlimab in DLL3-positive SCLC or other neuroendrocine tumors	Recruiting
NCT05963867[2]	1	BI 764532 biodistribution and tumor uptake in SCLC or neuroendrocine carcinoma	Not yet recruiting
DAREON-9[3]	1b	BI 764532 dose escalation study in combination with topotecan in 2L SCLC	Not yet recruiting
DAREON-5[4]	2	BI 764532 dose selection study in patients with relapsed/refractory SCLC or neuroendocrine carcinoma	Not yet recruiting

1. ClinicalTrials.gov, NCT05879978 (accessed August 2023; 2. ClinicalTrials.gov, NCT05963867 (accessed August 2023);
3. ClinicalTrials.gov, NCT05990738 (accessed August 2023); 4. ClinicalTrials.gov, NCT05882058 (accessed August 2023).

*According to ClinicalTrials.gov.

CRS is a systemic inflammatory response

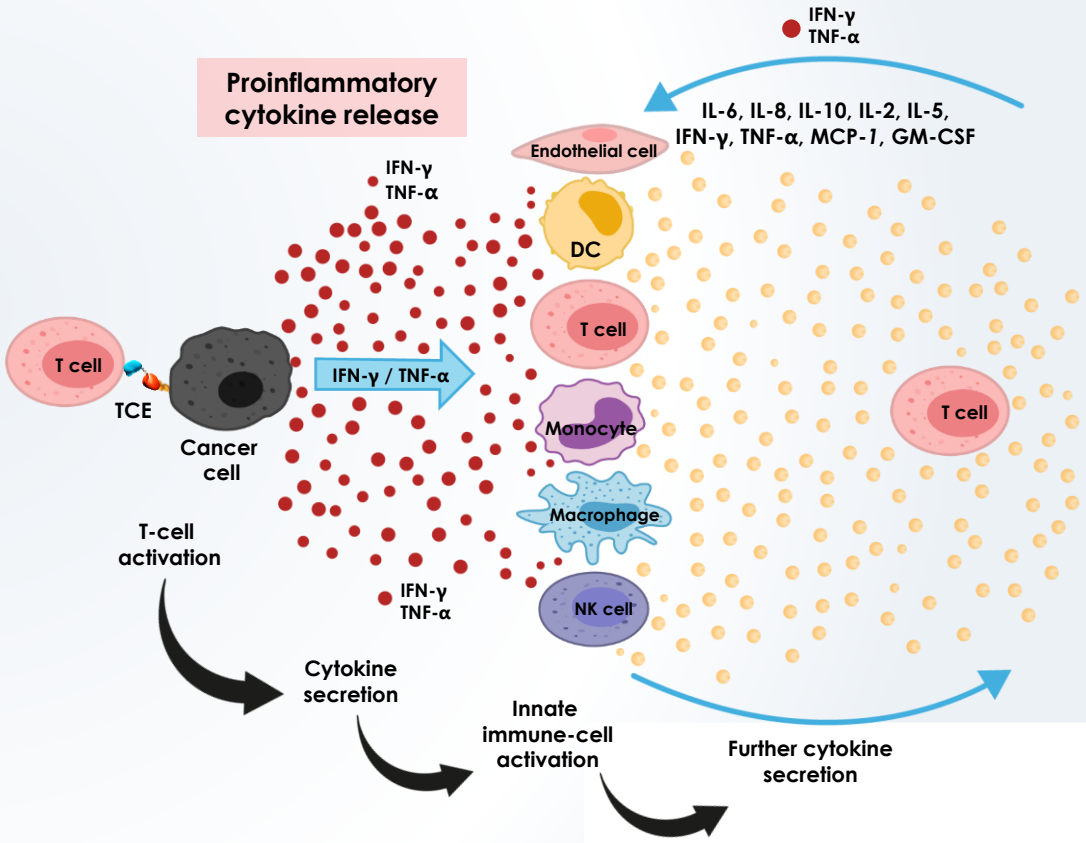
- T-cell immunotherapies may cause CRS[1,2]
- Proposed mechanism:[1,2]

Activation of T cells
± other effector cells

⇩

Release of
pro-inflammatory
cytokines

Pathophysiology of immunotherapy-induced CRS[1,2]



CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DC, dendritic cell; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; NK, natural killer; TCE, T-cell engager; TNF, tumor necrosis factor.

1. Shimabukuro-Vornhagen A, et al. J Immunother Cancer 2018;6:56;
2. Cosenza M, et al. Int J Mol Sci 2021;22:7652.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

The pathophysiology of ICANS is poorly understood[1]

Proposed mechanism[2]:

Systemic inflammation
+
Cytokine production

⇩

Endothelial cell activation

⇩

Blood-brain barrier disruption

⇩

Elevated cytokine levels in CSF

Proposed pathophysiology of ICANS[3]

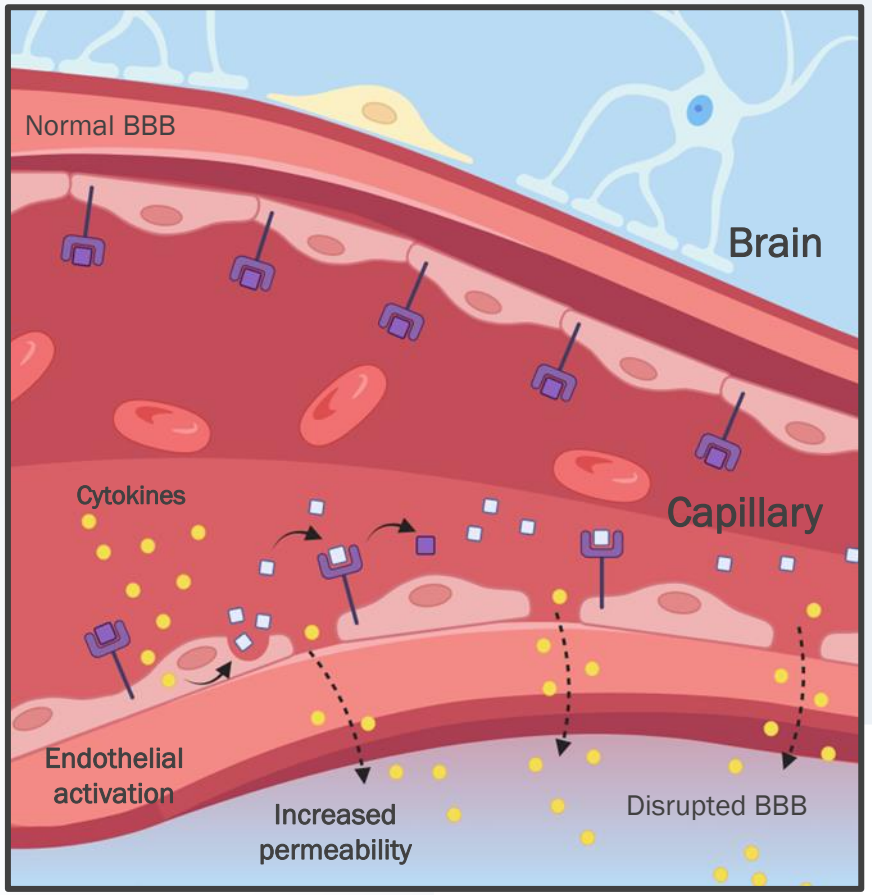


Figure created with BioRender.com

1. Morris EC, et al. Nat Rev Immunol 2022;22:85–96;
2. Maus MV, et al. J Immunother Cancer 2020;8:e001511;
3. Rice J, et al. Curr Treat Options Neurol 2019;21:40.

BBB, blood-brain barrier; CSF, cerebrospinal fluid; ICANS, immune effector cell–associated neurotoxicity syndrome; IL, interleukin; TNF, tumor necrosis factor.

Phase 1 DeLLphi-300: tarlatamab in relapsed/refractory SCLC

Cytokine release syndrome

Patients (N=107)	All grades	Grade 1–2	Grade 3	Grade 4	Grade 5
CRS*, n (%)	56 (52)	55 (51)	1 (1)	0	0

Median duration of CRS was 3 days (IQR 2–4 days])

Most CRS events were grade 1–2, occurred in the first 30 days†, and resolved in all cases

CRS events were generally manageable with observation and adequate supportive care, if needed (antipyretics, IV fluids, and corticosteroids)

Tocilizumab was administered to 8/107 patients (7.5%)

Data cut-off 19 July 2022; median follow-up: 8.7 months (range 0.2–31.8)

*CRS based on AMQ narrow search, which includes cytokine abnormal, cytokine release syndrome, cytokine storm, and cytokine test.

†One cycle = 28 days.[2]

AE, adverse event; AMQN, Amgen MedDRA Query narrow; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; G-CSF, granulocyte colony stimulating factor; ICANS, immune effector cell-associated neurotoxicity syndrome; IV, intravenous.

1. Paz-Ares L, et al. J Clin Oncol 2023;41:2893–903;
2. Paz-Ares L, et al. J Clin Oncol 2023;41:2893–903 (suppl protocol).

Phase 1 DeLLphi-300: tarlatamab in relapsed/refractory SCLC

Ad-hoc analysis assessing ICANS and associated neurological events

Ad-hoc safety analysis was assessed analyzing 103 patients dosed at 10 mg and 100 mg in DeLLphi 300

TRAE (N=103)	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Any ICANS and associated neurological events*, n (%)	11 (11)	3 (3)	4 (4)	3 (3)	1 (1)

- The most common ICANS and associated neurological events included encephalopathy, muscular weakness, and immune effector cell-associated neurotoxicity syndrome

Data on File, Amgen

Data cut-off: 27 January 2023

*medDRA 25.1 including 58 preferred terms.

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DS-7300 (B7-H3 DXd Antibody Drug Conjugate [ADC]) Shows Durable Antitumor Activity in Advanced Solid Tumors: Extended Follow-up of a Phase 1/2 Study

Toshihiko Doi,[1] Manish R. Patel,[2,3] Gerald S. Falchook,[4] Takafumi Koyama,[5] Claire Friedman,[6] Sarina A. Piha-Paul,[7] Martin Gutierrez,[8] Raghad Abdul-Karim,[9] Mark Awad,[10] Douglas Adkins,[11] Shunji Takahashi,[12] Shigenori Kadowaki,[13] Ben Cheng,[14] Naoko Okamoto,[14] Abderrahmane Laadem,[14] Naoto Yoshizuka,[14] Meng Qian,[14] Ololade Dosunmu,[3] Hendrik-Tobias Arkenau,[15] Melissa Johnson[3]

[1]National Cancer Center Hospital East, Chiba, Japan; [2]Florida Cancer Specialists and Research Institute, Sarasota, FL, USA; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; [5]National Cancer Center Hospital, Tokyo, Japan; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [7]University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [8]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [9]Henry Ford Health System, Detroit, MI, USA; [10]Dana-Farber Cancer Institute, Boston, MA, USA; [11]Washington University School of Medicine, St. Louis, MO, USA; [12]Japanese Foundation for Cancer Research, Tokyo, Japan; [13]Aichi Cancer Center Hospital, Aichi, Japan; [14]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [15]Sarah Cannon Research Institute and University College London, London, UK

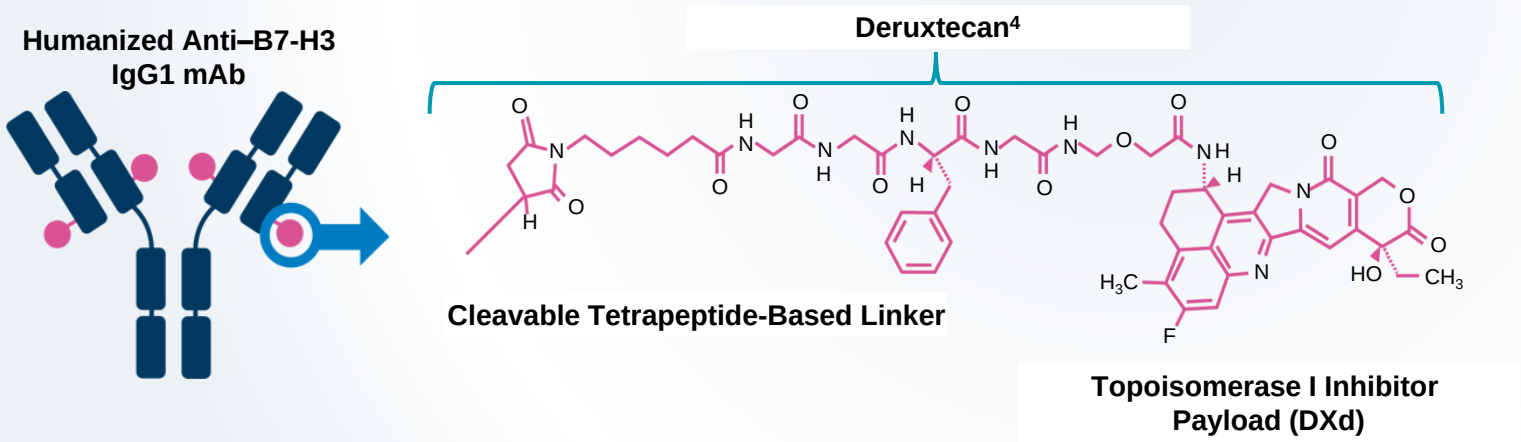
Ifinatamab Deruxtecan (I-DXd/DS-7300) in SCLC[1]

Ifinatamab deruxtecan (I-DXd) is an ADC with 3 components

A fully human anti-B7-H3 IgG1 mAb attached to

A topoisomerase I inhibitor payload and an exatecan derivative via

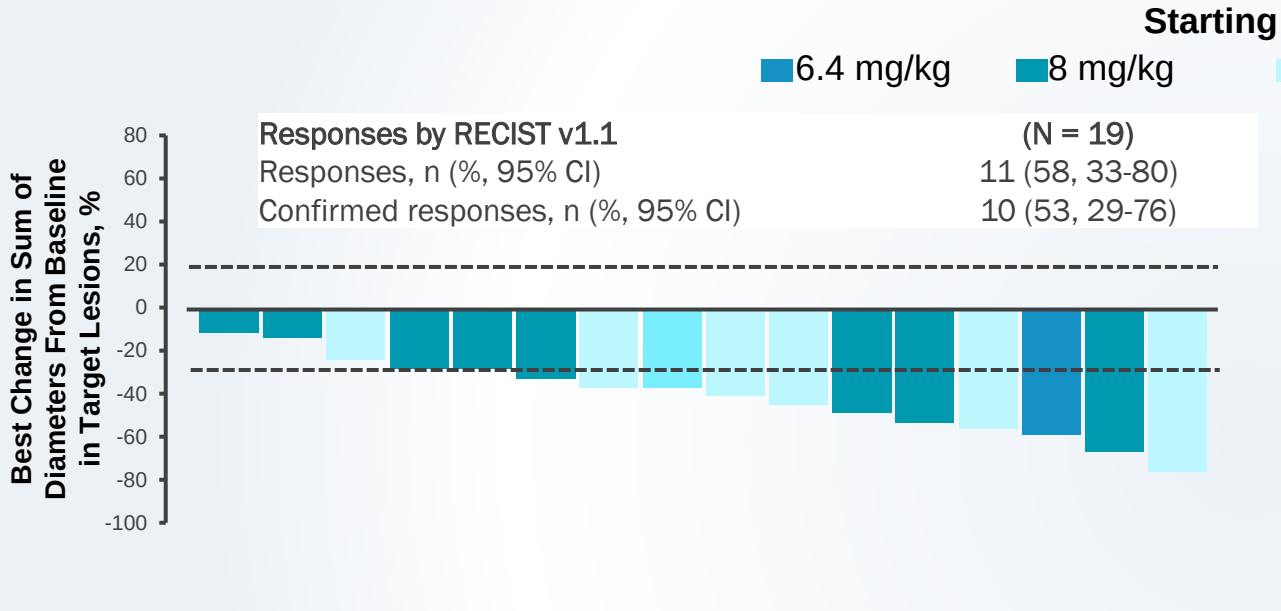
A tetrapeptide-based cleavable linker

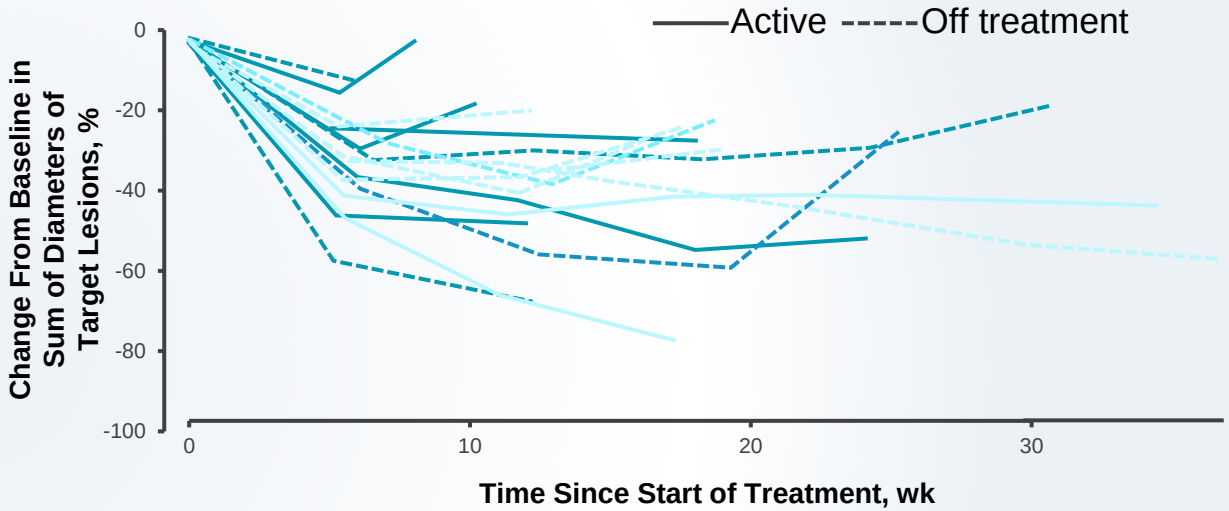


- Payload mechanism of action: topoisomerase I inhibitor
- High potency of payload
- Optimized DAR ~4
- Payload with short systemic half-life
- Stable linker payload
- Tumor-selective cleavable linker
- Bystander antitumor effect

Ifinatamab Deruxtecan (I-DXd/DS-7300) in SCLC: Antitumor Activity[1]

DS-7300 Phase 1/2 Study: Antitumor Activity in SCLC Subset[1]





	Part 1 Escalation					Part 2 Expansion	Study Total
	4.8 mg/kg (n = 5)	6.4 mg/kg (n = 8)	8.0 mg/kg (n = 19)	12.0 mg/kg (n = 33)	16.0 mg/kg (n = 16)	12.0 mg/kg (n = 66)	(N = 147)
Treatment duration, median (range), wk	9 (3-15)	14 (3-49)	15 (0-51)	13 (0-59)	14 (0-43)	9 (0-48)	12 (0-59)
Any TEAE, n (%)	5 (100)	8 (100)	19 (100)	32 (97)	16 (100)	64 (97)	144 (98)
TEAE with CTCAE grade ≥3	1 (20)	1 (13)	8 (42)	14 (42)	14 (88)	28 (42)	66 (45)
TEAE associated with drug discontinuation	0	0	4 (21)	2 (6)	2 (13)	3 (5)	11 (8)
TEAE associated with dose interruption	1 (20)	0	0	11 (33)	3 (19)	16 (24)	31 (21)
TEAE associated with dose reduction	0	0	2 (11)	4 (12)	5 (31)	7 (11)	18 (12)
Treatment-related TEAE associated with death	0	0	0	0	1 (6)	0	1 (1)

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Sacituzumab govitecan as second-line treatment for extensive stage small cell lung cancer

Preliminary results from the phase 2 TROPiCS-03 basket trial

Afshin Dowlati,[1] Andres Cervantes,[2] Sunil Babu,[3] Erika Hamilton,[4] Shu Fen Wong,[5] Andrea Tazbirkova,[6] Ivana Gabriela Sullivan,[7] Cédric van Marcke,[8] Antoine Italiano,[9] Jilpa Patel,[10] Sabeen Mekan,[10] Tia Wu,[10] Anne C. Chiang[11]

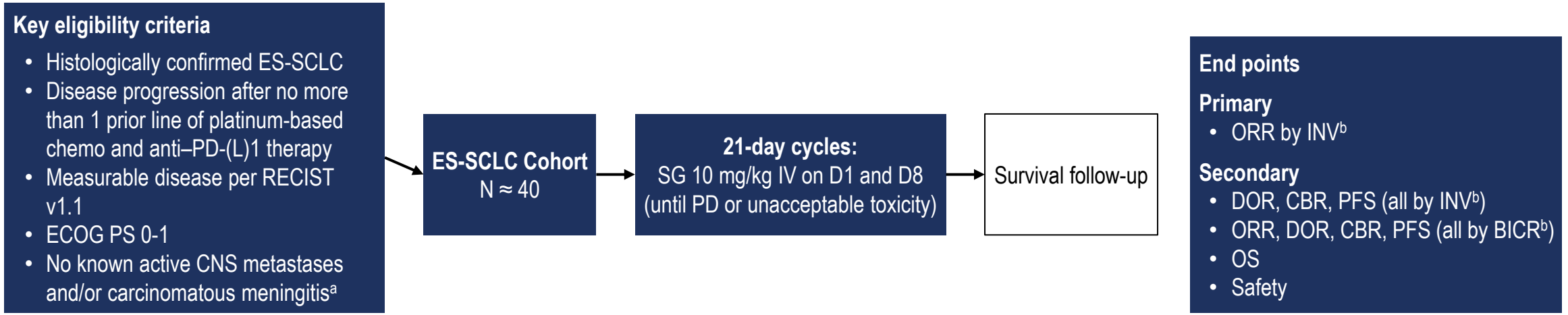
[1]University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; [2]INCLIVA Instituto de Investigación Sanitaria, University of Valencia, Valencia, Spain; [3]Fort Wayne Medical Oncology and Hematology, Fort Wayne, IN, USA; [4]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [5]Andrew Love Cancer Centre, Geelong, Australia; [6]Pindara Private Hospital, Benowa, Queensland, Australia; [7]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [8]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [9]Institut Bergonié, Bordeaux, France; [10]Gilead Sciences, Inc., Foster City, CA, USA; [11]Yale School of Medicine, New Haven, CT, USA

Presenter: Afshin Dowlati, MD

Saturday, October 21, 2023, 14:55-15:00
FPN: 1990MO

Background and study design

- Treatment options for patients with relapsed SCLC are limited[1]
- Sacituzumab govitecan is a Trop-2–directed ADC approved globally for the treatment of 2L+ mTNBC and pretreated HR+/HER2– mBC[2,3] and received accelerated approval in the United States for 2L mUC[3]
- The ongoing, open-label, multicohort, phase 2 TROPiCS-03 study (NCT03964727) is evaluating SG in patients with metastatic or locally advanced solid tumors



- At data cutoff (27 July 2023), median follow-up was 5.1 months (range, 1.9-12.2)

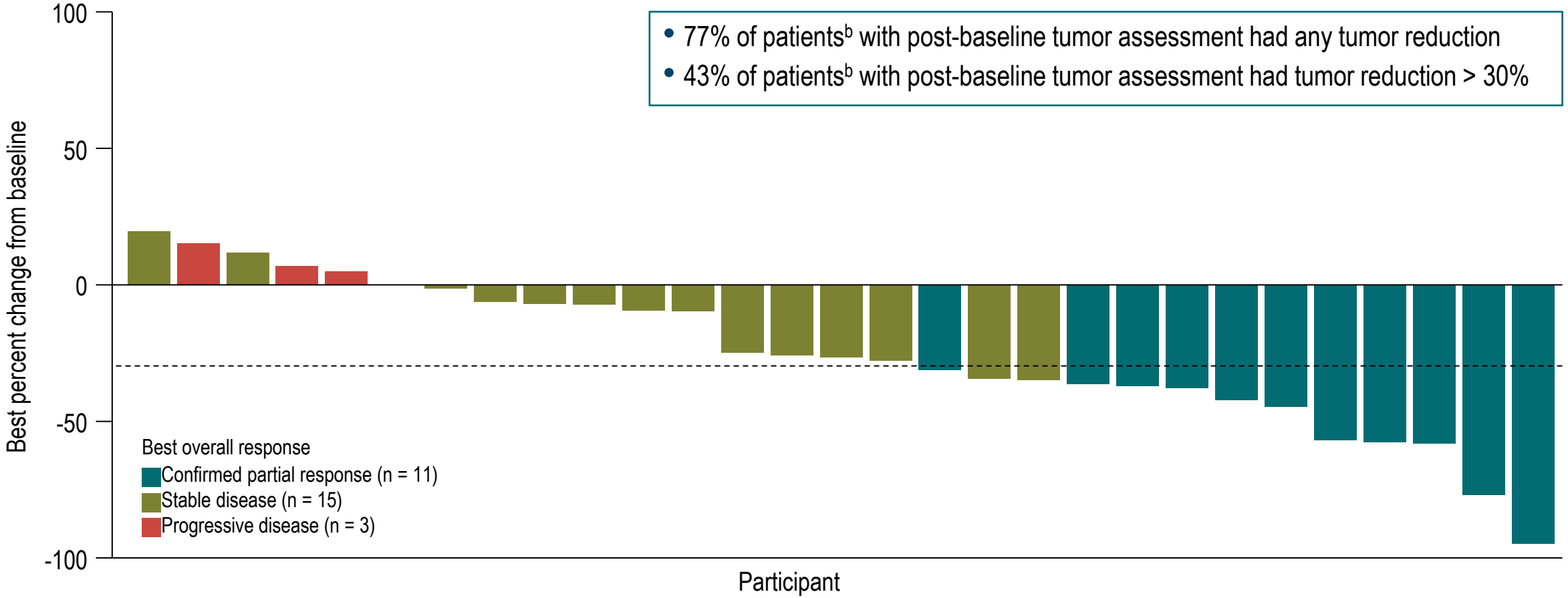
2L, second-line; ADC, antibody-drug conjugate; BICR, blinded independent central review; CBR, clinical benefit rate; CNS, central nervous system; D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive stage small cell lung cancer; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; INV, investigator; IV, intravenous; mBC, metastatic breast cancer; mTNBC, metastatic triple-negative breast cancer; mUC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SCLC, small cell lung cancer; SG, sacituzumab govitecan; Trop-2, trophoblast cell surface antigen 2. [a]Patients with stable CNS disease for at least 4 weeks prior to the first study dose and all neurologic symptoms returned to baseline may be included in the study. All patients with carcinomatous meningitis are excluded from the study regardless of clinical stability. [b]Per RECIST v1.1. **1.** Dingemans AC, et al. *Ann Oncol.* 2021;32(7):839-853. **2.** TRODELVY® (sacituzumab govitecan-hziy) [summary of product characteristics]. Gilead Sciences Ireland UC, Carrigtohill, Ireland; July 2023. **3.** TRODELVY® (sacituzumab govitecan-hziy) [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; June 2023

Efficacy by investigator assessment

Efficacy by INV[a]	ES-SCLC N = 30[b]
ORR [Confirmed CR + PR] **(95% CI), %**	37 (20-56)
BOR, n (%)	
Confirmed PR	11 (37)
SD	15 (50)
PD	3 (10)
DCR [Confirmed CR + PR + SD] **(95% CI), %**	87 (69-96)
CBR [Confirmed CR + PR + SD ≥ 6 months] **(95% CI), %**	40 (23-59)
Median DOR (95% CI),[c,d] months	6.3 (2.7-NR)
DOR rate at 6 months (95% CI),[c,d] %	63 (14-89)

Patients without post-baseline response assessments were counted as not assessed (n = 1). BOR, best overall response; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; ES-SCLC, extensive-stage small cell lung cancer; INV, investigator assessment; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease. [a]Per RECIST v1.1. [b]Includes patients enrolled on or before 27 April 2023. [c]Evaluated in patients with a confirmed CR or PR. [d]Based on Kaplan-Meier estimates.

Best percent change from baseline in target lesions[a]

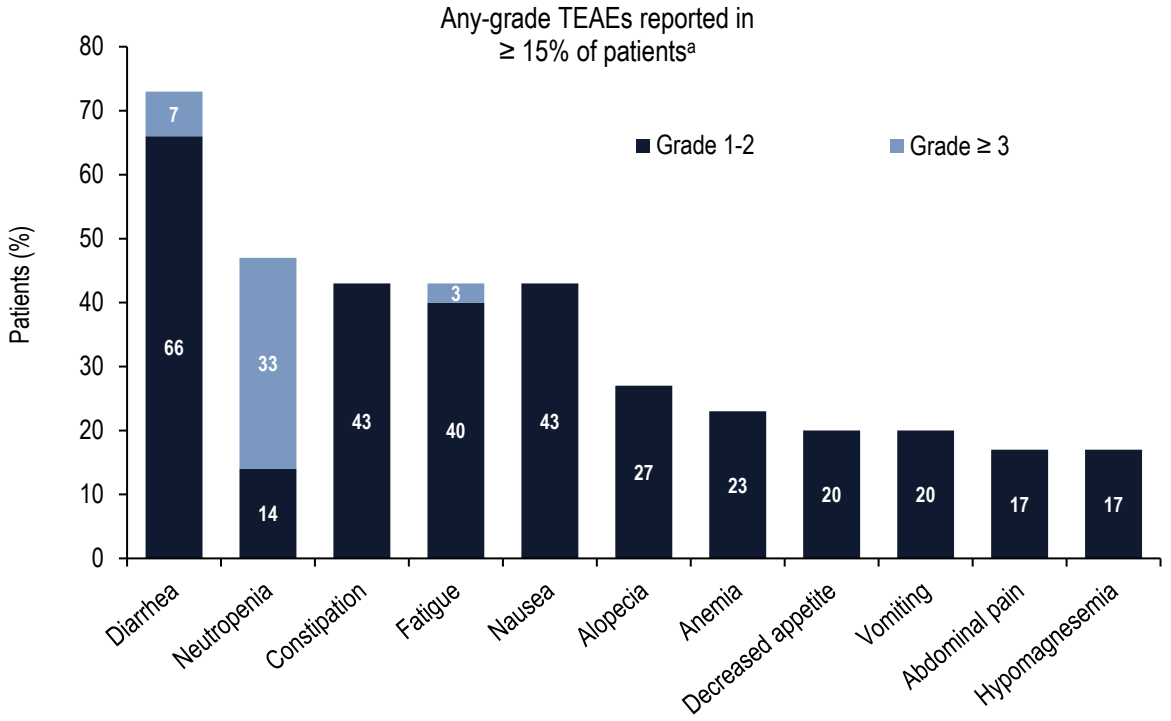


Includes patients enrolled on or before 27 April 2023. RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. [a]By investigator assessment per RECIST v1.1. [b]Percentages were calculated using the total number of patients (N = 30).

Safety summary

The adverse event profile observed in this trial was consistent with the observed safety of SG in other tumor types

Safety-evaluable patients, n (%)	ES-SCLC N = 30[a]
Any-grade TEAEs	30 (100)
Related to study treatment	28 (93)
Grade ≥ 3 TEAEs	18 (60)
Related to study treatment	15 (50)
Serious TEAEs	9 (30)
Related to study treatment	4 (13)
TEAEs leading to dose reduction	8 (27)
TEAEs leading to discontinuation	0
Related to study treatment	0
TEAEs leading to death	0
Related to study treatment	0



TEAE is defined as any adverse event with an onset date on or after the study treatment start date and no later than 30 days after the last dose of study treatment. ES-SCLC, extensive-stage squamous cell lung cancer; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event. [a]Includes patients enrolled on or before 27 April 2023.

ADCs in SCLC: Summary

Target	Payload/MOA	Agent	DAR	SCLC Activity RR, DOR	Source
TROP2	SN-38; topo I inhibitor Deruxtecan; topo I inhibitor	Sacituzumab govitecan Datopotamab deruxtecan	~7-8 ~4	N = 50, ORR 14%; DOR 5.7 mo	NCT01631552 (Gray et al. CCR 2017) NCT03401385
B7-H3	Deruxtecan; topo I inhibitor	Ifinatamab deruxtecan	~4	N = 19, ORR 58%; DOR 5.5 mo	NCT04145622
SEZ6	Calicheamicin; induces DS breaks	ABBV-011 ABBV-706	~2	–	NCT03639194 NCt05599984
CEACAM5	Maytansinoid DM4; MT inhibitor	Tusamitamab ravtansine	~3.8	–	NCT02187848
B7-H3	Clezutoclax; BCL-2/XL inhibitor	Mirzotamab clezutoclax	–	–	NCT03595059

Conclusions

- Anti angiogenic agent combined with chemoimmunotherapy is a promising approach in treatment naïve patients
- Novel approach using BiTE platform to redirect anti tumor immune response will redefine management of relapsed SCLC
- Antibody-drug conjugates with potent payload against tumor specific targets are now in development
- Translational research to discover and validate new therapeutic targets is needed